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Patterns of Creatine Kinase Release During Acute Myocardial Infarction After Nonsurgical Reperfusion: Comparison With Conventional Treatment and Correlation With Infarct Size

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Coronary arteriography and biplane ventriculography were performed in 51 patients during the acute (mean of 6.6 hours after onset of symptoms) and chronic (1 to 3 months after admission) phase of myocardial infarction. Twenty-four patients were treated in a conventional manner. In 27 patients, reperfusion was achieved with intracoronary streptokinase after 24 ± 20 minutes of infusion. Peak creatine kinase and cumulative creatine kinase release were derived from serial creatine kinase measurements. Ejection fraction and the length of the akinetic or dyskinetic segments were calculated in the chronic phase.

The time interval between onset of symptoms and peak creatine kinase was significantly shorter for the streptokinase-treated patients as compared with the conventionally treated patients (13.5 ± 5.3 versus 22.9 ± 7.4 hours, p = 0.0001). Significant linear correlations were obtained for both streptokinase-treated and control patients, relating: 1) peak creatine kinase value to both length of the noncontracting segment and ejection fraction in the chronic phase, and 2) cumulative creatine kinase release to both length of the noncontracting segment and ejection fraction in the chronic phase. Patients treated with streptokinase experienced a relatively greater release of enzyme for a given infarct size as compared with those treated in a conventional manner. The difference in enzyme release between the two groups increased as infarct size increased.

These observations may be explained by enhanced washout of enzyme from the infarct zone, secondary to reperfusion after intracoronary streptokinase therapy. The variability in creatine kinase release observed in the streptokinase-treated patients with small infarcts suggests that prediction of infarct size for an individual patient from time-activity curves of creatine kinase release should be made with caution.

Shell and Sobel (1,2) developed a model for calculating infarct size using serial measurements of serum creatine kinase activity. Subsequent studies (3–9), however, suggested that different subsets of patients with myocardial infarction have diferent patterns of enzyme release.

This study describes the kinetics of creatine kinase release in patients who had successful reperfusion after receiving intracoronary streptokinase therapy during acute myocardial infarction. The pattern of creatine kinase release in the patients receiving streptokinase therapy was compared with that of patients given conventional therapy. An attempt was made to define the relation between creatine kinase release and angiographic estimates of infarct size for both groups of patients.

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Methods

Patients

Streptokinase group. Twenty-seven of 67 consecutive patients admitted with acute myocardial infarction, in whom the infarct vessel was recanalized by intracoronary streptokinase therapy, were included in this study. All 27 patients fulfilled the following criteria: 1) informed consent for cardiac catheterization and administration of intracoronary

medication was obtained; 2) the time from onset of chest pain to hospital admission was less than 24 hours in duration; 3) total occlusion of the infarct-related vessel was present at the time of initial angiographic visualization; 4) at the end of the streptokinase infusion there was prompt antegrade filling of the initially occluded vessel; 5) angiography was repeated during the chronic stage of infarction; 6) no surgical intervention was made between the initial angiogram and the repeat study; and 7) serial blood samples for creatine kinase assay were drawn. The remaining 40 patients were excluded from this analysis on the basis of the following exclusion criteria: 1) history of previous myocardial infarction; 2) cardiogenic shock; 3) recent intramuscular injection; 4) intraaortic balloon counterpulsation; 5) clinical signs of infarct extension or recurrent infarction during the study period; 6) demonstration of reocclusion of the infarct vessel at repeat angiography, in the chronic stage; and 7) inadequate number of blood samples drawn for serial creatine kinase analysis.

Comparison group. These patients were selected from 66 consecutive patients presenting with acute myocardial infarction who underwent initial angiography as part of a protocol undertaken before the advent of streptokinase therapy. No attempt was made to reopen the infarct vessel with a guidewire or intracoronary administration of drugs. Twenty-four of these 66 patients who met the same criteria as the streptokinase group formed the comparison group.

Study Protocol

Diagnosis of acute myocardial infarction. The diagnosis of acute myocardial infarction was determined on the basis of a history of chest pain lasting more than 30 minutes, and associated with electrocardiographic changes suggestive of acute ischemia in at least two leads (ST segment elevation or depression of at least 0.1 mV, loss of R waves or development of new Q waves, or both). The diagnosis was confirmed retrospectively in all patients by an increase of creatine kinase to at least twice the upper limit of normal. The onset of chest pain was determined by the same observer for all patients in both groups.

Coronary reperfusion technique. The method of initial angiography during the acute phase of an acute myocardial infarction and administration of intracoronary streptokinase has been described previously (10). Reperfusion was achieved by intracoronary streptokinase infusion (2,000 units/min) alone in 21 patients and combined with guidewire recanalization in 6 patients. Reperfusion was observed after 24 ± 20 (mean ± standard deviation) minutes of therapy in the group as a whole. A mean of 6.9 ± 6.3 hours elapsed between the onset of chest pain and recanalization. The total duration of streptokinase infusion was 64 ± 26 minutes.

Assessment of left ventricular function and infarct size. All patients in both groups underwent biplane left ventriculography before coronary arteriography during the acute and chronic stages of infarction. Ventricular volumes were calculated using the area-length formula of Dodge et al. (11). On the basis of systolic and diastolic ventricular volume measurements, ejection fraction in the acute and chronic stages was calculated. The length of any akinetic or dyskinetic segment was measured in centimeters using the method of Feild et al. (12). The severity of an intraluminal coronary artery narrowing was assessed using the criteria of Gensini (13).

Creatine kinase determination. Blood for creatine kinase assay was drawn immediately on admission, before any intervention and every 2 to 3 hours thereafter for at least 48 hours. Creatine kinase activity was assayed by the technique of Szasz et al. (14). Time-activity curves were constructed for each patient. From these curves peak creatine kinase activity was measured. Total creatine kinase release was calculated according to the method of Norris et al. (3).

Differences between study and control groups (Table 1). The two groups were comparable in age, sex, duration of symptoms before initial angiography, localization of infarct vessel, extent of coronary artery disease, presence of collateral circulation, initial ejection fraction and the initial length of noncontracting segments. Both groups of patients received intravenous nitroglycerin for at least 48 hours. The duration of symptoms from onset of chest pain to initial angiography in the streptokinase group and the control group was 5.9 ± 6.3 and 7.4 ± 4.5 hours, respectively (probability [p] = not significant [NS]).

The groups differed in the following variables: 1) the initial creatine kinase values for the comparison group were slightly higher than those of the streptokinase group (179 ± 170 versus 100 ± 79 U/liters [$p = 0.05$]); 2) only patients in the streptokinase group received prednisolone, 747 mg intravenously; aspirin, 1 g intravenously and nifedipine, 10 mg sublingually; 3) all patients in the streptokinase group received at least 72 hours of a continuous intravenous infusion of heparin of 20,000 or more U/day followed by oral coumadin. Twenty patients in the comparison group received a continuous infusion of heparin, 12 of whom remained on oral coumadin therapy while 4 patients received subcutaneous heparin, 20,000 U/day, until they began to walk; 4) repeat angiography was performed at a later date in the control group than in the streptokinase group (63 ± 45 versus 33 ± 54 days, respectively [$p < 0.05$]).

In the streptokinase group of 27 patients, angiography during the chronic stage revealed 18 patients with a 90% or greater residual stenosis, and 9 patients with a less than 90% residual stenosis in the infarct vessel. Ten of the 24 patients in the comparison group demonstrated spontaneous recanalization of the infarct vessel at repeat angiography

Table 1. Clinical and Angiographic Data

	Streptokinase Group (n = 27 patients)	Control Group (n = 24 patients)
Sex		
Male	24	21
Female	3	3
Age (yr)	55	54
Duration of symptoms prior to angiography (hours)	5.9 ± 6.3	7.4 ± 4.5
CK on admission (U/L)	100 ± 79	179 ± 170*
Infarct vessel		
LAD	13	11
LCx	4	7
RCA	10	6
Patients with collateral channels to the infarct (no.)	13	12
Extent of CAD		
1 vessel disease	14	8
2 vessel disease	6	10
3 vessel disease	7	6
Time from initial to repeat angiography (days)	33 ± 54	63 ± 55*
Ejection fraction		
Initial†	54 ± 11	52 ± 10
Chronic	62 ± 9	48 ± 14*
Noncontracting segment		
Initial (cm)	7.1 ± 6.5	9.0 ± 5.0
Chronic	2.2 ± 4.0	8.8 ± 6.9*

*Denotes that the difference between the two groups is statistically significant ($p < 0.05$). † Normal ejection fraction using biplane ventriculography is > 60%. CAD = coronary artery disease; CK = creatine kinase; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

during the chronic stage. Of these 10 patients, 6 had a greater than 90% residual stenosis.

Statistics. Data are presented as mean values ± standard deviation. The *t* test, paired *t* test and chi-square test were used to compare variables. A probability value of 0.05 or less was considered significant. Linear correlations and inverse regression techniques were used.

Results

There was a significant correlation between peak creatine kinase activity and cumulative kinase release in both groups of patients: streptokinase group, r = 0.97 and comparison group, r = 0.89, p = 0.0001.

Creatine kinase kinetics (Fig. 1). Peak creatine kinase activity was 766 ± 798 U/liter in the streptokinase group and 1,043 ± 538 U/liter in the comparison group (p = NS). The time elapsed between onset of symptoms and peak creatine kinase levels was significantly shorter for the streptokinase group (13.5 ± 5.3 versus 22.9 ± 7.4 hours [p = 0.0001]). In the streptokinase group peak creatine kinase was reached 6.5 ± 4.5 hours after recanalization. Total creatine kinase release was lower in the streptokinase group than in the comparison group but the difference did not reach statistical significance (1.058 ± 963 U/liter versus 1,571 ± 963 U/liter [p = NS]).

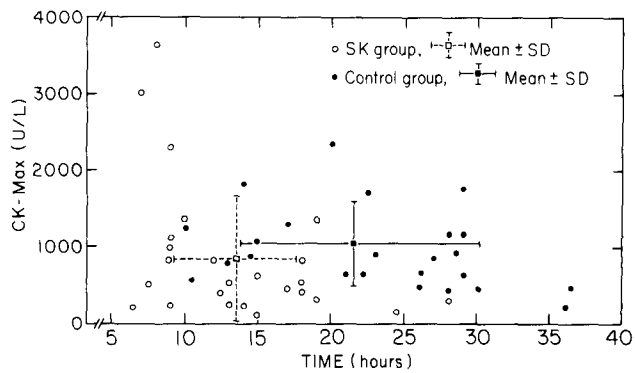
There were no significant differences with respect to infarct size or enzyme release between the 10 patients in the comparison group who demonstrated spontaneous recanalization and those with persistent occlusion.

Changes in left ventricular function and infarct size (Fig. 2 to 4). In the acute stage before any interventions, the ejection fraction and the length of the noncontracting segments of patients in the streptokinase group were comparable with those of the comparison group. However, the ejection fraction and the length of the noncontracting segments improved between acute and chronic angiography in the streptokinase group but not in the comparison group. Angiography in the chronic phase revealed significantly better function in the streptokinase group than in the conventionally treated group.

Correlation of peak creatine kinase and cumulative creatine kinase release with length of noncontracting segments and ejection fraction in the chronic stage. There was a significant linear correlation between peak creatine kinase and length of the noncontracting segment in both groups of patients. However, the slope of the regression line was significantly steeper for the streptokinase-treated patients (169 versus 44, p = 0.0001) (Fig. 2). In addition, there was a significant correlation between peak creatine kinase and ejection fraction in both groups of patients. The slope of this regression line was significantly steeper for the streptokinase group (−65 versus −28, p = 0.0001) (Fig. 3).

There was a significant linear correlation between total creatine kinase release and the length of the noncontracting

Figure 1. Time in hours from onset of symptoms to peak creatine kinase release (CK-Max). SD = standard deviation; SK = streptokinase.



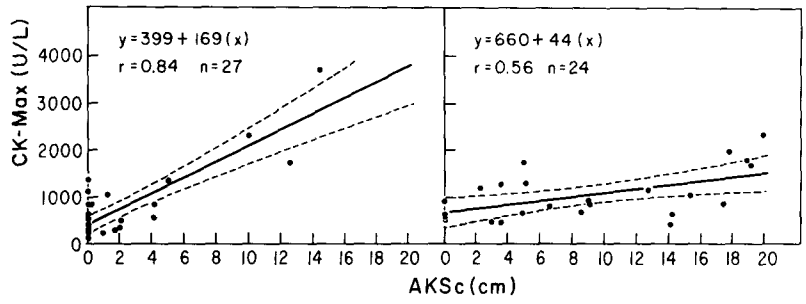


Figure 2. Correlation between peak creatine kinase (CK-Max) and the length of the noncontracting segment in the chronic stage (AKSc) in the streptokinase group (**left**) and the control group (**right**). **Dotted lines** represent the 95% confidence intervals.

segment in the streptokinase group and the comparison group. The slope of this line was significantly steeper for the streptokinase group (199 versus 85, p = 0.004) (Fig. 4). A significant correlation was also observed between cumulative creatine kinase release and ejection fraction in both groups. This line was steeper for the streptokinase group but the difference did not reach statistical significance (−73 versus −45, p = NS) (Fig. 5).

Discussion

Earlier time to peak creatine kinase activity. Previous studies using creatine kinase time-activity curves in patients with acute myocardial infarction (2,3) indicated that the average time from the onset of symptoms to peak creatine kinase activity varies from 16 to 30 hours. The data from our control group is in agreement with these studies.

In contrast, our patients with successful reperfusion after intracoronary administration of streptokinase demonstrated a significantly shorter time to peak creatine kinase activity of 13.5 hours. This finding, in human subjects, is in agreement with previous animal experiments that showed earlier times to peak creatine kinase after reperfusion after temporary coronary artery ligation (5,15). Recent reports (16–30) in human subjects also indicate that early recanalization during acute myocardial infarction results in an earlier time to peak creatine kinase (10 to 14 hours). Investigators in a randomized cooperative study using intravenous streptokinase observed a mean time of 15.7 hours to peak creatine kinase in patients who received therapy less than 3 hours after the onset of symptoms (21). This contrasts with a mean time of 20.8 hours to peak creatine kinase in their patients who received intravenous streptokinase therapy after 3 hours. Although they did not have angiographic correlations it is conceivable that the early institution of therapy resulted in the reopening of the infarct vessel in a fraction of the patients they studied.

It is conceivable that spontaneous recanalization, which occurred in 10 of the 24 control patients at some time between initial and repeat angiography, may have diminished the differences between our conventionally treated group and the streptokinase-treated group. However, comparison of the pattern of enzyme release in our conventionally treated patients with spontaneous recanalization with that in patients with persistent occlusion revealed no significant differences.

Increased creatine kinase release. The data derived from our study suggest that for infarcts of equal size, as assessed by length of akinetic or dyskinetic segment, there is a greater peak creatine kinase and total creatine kinase release in the patients treated with recanalization than in the conventionally treated group. This is in agreement with previous experimental work by Vatner et al. (5), who observed that for infarcts of equal size as measured at autopsy there was a relatively greater release of creatine kinase into the serum in dogs with reperfusion than in the dogs with permanent coronary occlusion. Schuster et al. (22) correlated infarct size, as measured pathologically, with creatine kinase release in human beings and observed a relatively greater release of creatine kinase for similar-sized infarcts in patients who demonstrated hemorrhagic necrosis. Hemorrhagic necrosis was presumed to be a marker of reperfusion. As suggested by previous investigators (5), a possible explanation for these observations of 1) an earlier time

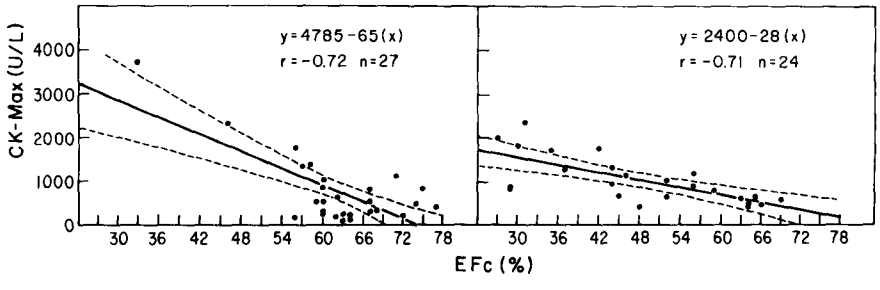


Figure 3. Correlation between peak creatine kinase (CK-Max) and the ejection fraction in the chronic stage (EFc) in the streptokinase group (**left**) and in the control group (**right**). **Dotted lines** represent the 95% confidence intervals.

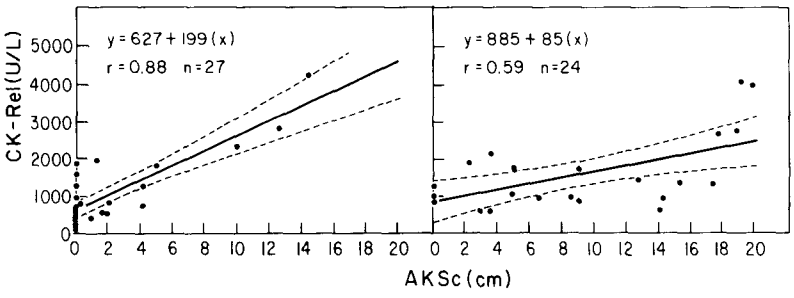


Figure 4. Correlation between cumulative creatine kinase release (CK-Rel) and the length of the akinetic segment in the chronic stage (AKSc) in the streptokinase group (**left**) and the control group (**right**). **Dotted lines** represent the 95% confidence intervals.

to peak creatine kinase activity, and 2) a greater cumulative release of creatine kinase for infarcts of equal size is that there is a washout effect resulting from reperfusion.

The original formula of Sobel and colleagues (2) for estimating infarct size from time-activity curves of creatine kinase release assumed a constant serum entry ratio of creatine kinase into the peripheral circulation irrespective of the size of the infarction or the presence of collateral blood flow. Experimental studies by Cairns et al. (7) comparing multiple small infarcts with a single large infarct in a dog model demonstrated variable serum entry of creatine kinase depending on the size of the infarct. Swain et al. (8), also using a dog model, suggested that larger infarcts, which have a large central zone of severely reduced regional blood flow, will release disproportionately less enzyme into the peripheral circulation.

Patients with a large infarct in whom reperfusion is achieved should, theoretically, have an improved blood flow to the central ischemic zone, unless there is a "no reflow" phenomenon. Our finding that the difference in enzyme release between patients treated with reperfusion and conventionally treated patients increases with increasing infarct size suggests that: 1) a no reflow phenomenon did not occur in our patients with reperfusion, and 2) in patients without reperfusion the serum entry ratio of creatine kinase into the peripheral circulation is inversely related to infarct size.

Our study demonstrated some degree of variability in the values for peak creatine kinase and cumulative creatine kinase release for patient in the streptokinase group with a small infarct. A possible explanation for the increased variability may be that determination of extent of tissue damage based on length of noncontracting segment may be less accurate in patients with a small infarct.

Limitations of the study. This study was retrospective and nonrandomized and therefore subject to several limitations. Only patients in the streptokinase group received prednisolone, aspirin and nifedipine. However, a recent controlled study by Madias and Hood (23) found no significant difference in peak creatine kinase between patients who received corticosteroids as compared with a control group. In addition, we are not aware of any direct effect of aspirin and nifedipine on creatine kinase release other than their possible role in preserving the patency of the coronary artery after streptokinase infusion. Patients in our comparison group had repeat angiography at a later time than those in the streptokinase group. It is not likely that the delay in evaluation of ejection fraction in the chronic stage in our comparison group would have exaggerated the difference in angiographic estimates of infarct size. Borer et al. (24) observed a slight improvement in ejection fraction in patients during the chronic phase of myocardial infarction. Our comparison group had a higher initial creatine kinase value. This initial elevation in some of our conventionally treated patients did not preclude calculation of peak creatine kinase or cumulative creatine kinase release. It is possible that our correlations may have been improved had the more specific marker creatine kinase-MB been used. However, none of our patients received intramuscular injections or underwent defibrillation.

Clinical implications. Patients in whom successful recanalization is achieved by intracoronary streptokinase therapy during acute myocardial infarction have an earlier rise to peak creatine kinase activity and a relatively greater cumulative release of creatine kinase as compared with conventionally treated patients with an infarct of similar size. It is possible that the pattern of early enzyme release may

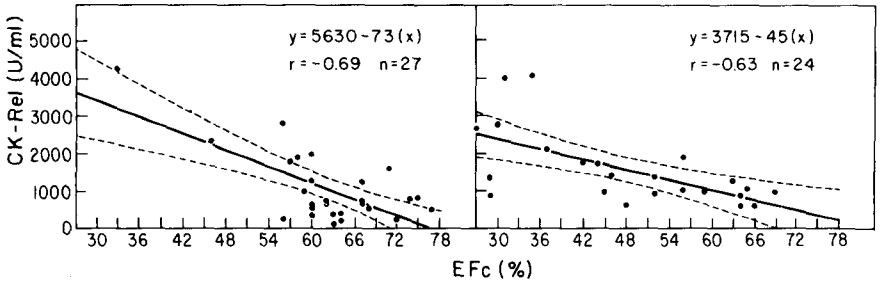


Figure 5. Correlation between cumulative creatine kinase release (CK-Rel) and the ejection fraction in the chronic stage (EFc) in the streptokinase group (**left**), and the control group (**right**). **Dotted lines** represent the 95% confidence intervals.

be used as a noninvasive marker for early coronary recanalization (25). In spite of a relatively large cumulative release of enzyme, patients experiencing early recanalization may have a better prognosis. The variability in creatine kinase release observed in our streptokinase-treated patients with a small infarct suggests that prediction of infarct size for an individual patient from time-activity curves of creatine kinase release should be made with caution.

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